PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference AHB/FP6164701	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/08926	International filing date *(day/month/year)* 12.08.2003	Priority date *(day/month/year)* 14.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K39/385		
Applicant AVIDIS SA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12.03.2004	02.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Nooij, F Telephone No. +31 70 340-3267

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/08926

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-47 as originally filed

Claims, Numbers

1-21 as originally filed

Drawings, Sheets

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11, 21 (both partially)

because:

☒ the said international application, or the said claims Nos. 11, 21 (both partially, for reasons of industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	16
	No:	Claims	1-15,17-21
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-10,12-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims **11** and **21** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO 00 69907 A (MEDICAL RESEARCH COUNCIL) 23 November 2000 (2000-11-23) cited in the application

D2: WO 91 11461 A (BIOGEN, INC.) 8 August 1991 (1991-08-08) cited in the application

D3: GB-A-2 282 813 (MERCK & CO., INC.) 19 April 1995 (1995-04-19)

D4: E. SHINYA ET AL.: 'In-vivo delivery of therapeutic proteins by genetically-modified cells: comparison of organoids and human serum albumin alginate-coated beads.' BIOMEDICINE AND PHARMACOTHERAPY, vol. 53, December 1999 (1999-12), pages 471-483, XP002231127, Paris, France. cited in the application

D5: WO 01 00231 A (SMITHKLINE BEECHAM BIOLOGICALS) 4 January 2001 (2001-01-04)

D6: A. KOL ET AL.: 'Cutting edge: Heat shock protein (HSP) 60 activates the innate immune response: CD14 is an essential receptor for HSP60.' THE JOURNAL OF IMMUNOLOGY, vol. 164, no. 1, 1 January 2000 (2000-01-01), pages 13-17, XP002262385, Baltimore, MD, USA

1. NOVELTY (Article 33(2) PCT)

1.1 *D1* discloses a protein scaffold, e.g. cpn10 (see page 12, lines 5-6), which may incorporate an adjuvant on the scaffold, together with an immungen (see page 14, lines 29-30). Used for vaccination. It also mentions a heterologous polypeptide, which may comprise other non-amino acid components (see page 9, line 28 - page 10, line 2), and which may be inserted into the cpn10 family polypeptide (see page 4, lines

30-31). Also DNA vaccination disclosed. Hsp60 may act as a scaffold with adjuvant properties, i.e. scaffold is also adjuvant (see page 20, line 20 - page 21, line 12). According to *D6* (see abstract), hsp60 can activate the immune response via CD14, present on monocytes and macrophages, i.e. antigen-presenting cells.

1 2 *D2* discloses a protein scaffold, e.g. C4bp, fused to functional moieties, e.g. antigens for vaccination purposes. Adjuvant may be included. Heteromultimeric fusion proteins comprising C4bp and CD4. The latter is a ligand for MHC class II molecules which are expressed a.o. on activated T cells. Also expression vectors and prokaryotic and eukaryotic host cells have been disclosed.

1.3 *D3* discloses annular antigen scaffolds comprising thioether linkages. Adjuvants may also be coupled to this complex (see the examples and claims).

1.4 *D4* disclosesa.o. multimeric CD4-C4bp fusion proteins. Transfected eukaryotic 293 host cells. Also gene therapy (see abstract).

1.5 *D5* discloses a fusion protein comprising HBsAg and malaria sequences. Maybe combined with several adjuvants.

1.6 In view of the prior art, the subject-matter of present claims **1-15** and **17-21** is not new in the sense of Article 33(2) PCT.

2. INVENTIVE STEP (Article 33(3) PCT)

2.1 Present dependent claim **16** does not contain any features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of inventive step, the reasons being as follows:

D4 discloses that soluble multimeric CD4-C4bp was produced by eukaryotic 293 cells implanted in organoids at levels of 2,300 ng/mL, i.e. 2.3 mg/L.

The choice for production of the multimeric fusion protein in prokaryotic host cells would be one that is merely one of several straightforward possibilities from which the skilled person would select, in accordance with the circumstances, without the

exercise of inventive skill, in order to solve the problem posed.

3. FURTHER REMARKS

3.1 For the assessment of the present claims **11** and **21** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3.2 The phrase "... a polypeptide which is a ligand for CD21 or a cell surface molecule on B cells or T cells or follicular dendritic or other antigen-presenting cells..." used in present claims **2, 12, 13** and **18**, is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter unclear (Article 6 PCT):
From the present wording of said claims, it is not clear whether the polypeptide can be a cell surface molecule (**itself**)...etc., or that the polypeptide can be **a ligand** for a cell surface molecule... etc.